THE MEDICAL LETTER

a non-profit publication

on Drugs and Therapeutics

Published by Drug and Therapeutic Information, Inc., 136 East 57th Street, New York 22, New York

Vol. 1, No. 24 December 11, 1959

ACTASE AND STREPTOKINASE

Actase (Ortho), a preparation of plasmin (fibrinolysin) produced by activating human plasminogen with streptokinase in vitro, has been described by the manufacturer as opening "a new epoch in the treatment of thromboembolic disorders," and it has been hailed by the press as a remarkable new agent for dissolving life-threatening blood clots. A reliable means of dissolving already formed clots in blood vessels is an exciting therapeutic prospect. As for Actase, its effectiveness appears to be slight, unpredictable and of brief duration.

A series of generally favorable studies of Actase were reported in Angiology (No. 4, Part 2, Aug. 1959). The studies included many cases in which it was used with apparent success in venous thrombosis and pulmonary embolism; but none of the studies were controlled. Most of the patients received anticoagulants in addition to Actase.

ACTASE WITH ANTICOAGULANTS - One small controlled study suggests that combined fibrinolysin-anticoagulant therapy leads to a more rapid resolution of episodes of acute phlebitis than anticoagulant drugs alone (K. M. Moser, et al., 32nd Session, Am. Heart Ass'n, Oct. 1959). Unfortunately, the control group was an unusual one in that four of the 20 patients had pulmonary infarcts. The authors note a reduction in the average duration of immobilization with Actase; the longer duration for the control group was almost certainly affected by the high incidence of pulmonary infarction in that group.

One study (J. L. Villavicencio and R. Warren, Angiology, 10:263, 1959) showed dramatic improvement in clinical signs in only one of 14 patients receiving Actase. In animal experiments, these authors dissolved clots successfully by introducing Actase into the affected vessel in concentrations 15 to 20 times those obtained from the recommended dosage in man.

Villavicencio and Warren see a great future for plasmin therapy of thromboses, once the substance has been purified. It is possible, however, that Actase owes whatever activity it has to its impurities. These impurities include a considerable amount of pyrogenic material, and it is now known that pyrotherapy alone can dissolve venous clots. Since the amount of plasmin in Actase is extremely low, the therapeutic effect of the preparation may be due not to the plasmin, but to the chills and fever produced in some patients by the impurities.

Plasmin preparations of much higher purity have, however, been prepared for experimental purposes, making it possible to give very much larger doses than the recommended doses of Actase (J. L. Ambrus, et al., Ann. N.Y. Acad. Sci., 68:97, 1957; E. E. Cliffton, et al., Ann. N.Y. Acad. Sci., 68:209, 1957), and it has been demonstrated that large doses are effective in the absence of pyrogenic reactions. In appraising the action of Actase it is important to realize what "large" dosage of plasmin means. J. E. Sokal, et al. (JAMA, 168:1314, 1958) and Ambrus, et al. found that consistent fibrinolysis could be obtained with a dosage of 15 Loomis units of plasmin per kilogram of body weight. One 50,000-unit dose of Actase is equivalent to 0.6 Loomis units. Thus the dose given by these investigators is about 2,000 times the dose recommended for Actase. (The cost of Actase is about $45 to $50 per 50,000-unit dose.)

STREPTOKINASE - The physiology of the fibrinolytic enzymes is complex, and experts differ not only as to their action but also as to which enzyme is the most effective clot-dissolving agent. When streptokinase itself is injected into the blood stream, it exerts a fibrinolytic effect by combining with natural plasminogen in the clot, forming fibrin-destroying plasmin at the point where it is needed (N. Alkjaersig and S. Sherry, J. Clin. Invest., 38:1086, 1959). Large doses must be used, however, because of the presence of anti-streptokinase in the blood. Also, because streptokinase promotes the emergence in the blood of anti-thrombin factors, hemorrhagic complications have been much more striking with streptokinase than with plasmin.

Purification of streptokinase is a difficult procedure, and only amounts sufficient for investigation have been prepared. One such investigation indicates that this substance can produce a sustained thrombolytic state in man, even in acute myocardial infarction (A. P. Fletcher, et al., J. Clin. Invest., 38:1096 and 1111, 1959). The effectiveness of streptokinase is further indicated by a report of a unique experimental study in which thromboses were induced in superficial veins of human volunteers (A. J. Johnson and W. R. McCarty, J. Clin. Invest., 38:1627, 1959). Streptokinase consistently destroyed the clots, as shown by inspection, palpation and venography.

Until a truly effective commercial preparation of a fibrinolytic or clot-dissolving agent is produced, whether with a potent plasmin, streptokinase or some other enzyme, the "new epoch" in the management of thromboembolic disorders can only remain as a hope and promise. For the present, the use of heparin and oral anticoagulant drugs for the prevention of clotting (see The Medical Letter, Nov. 13, 1959) is the only effective drug resource for the clinical management of thromboembolic disorders.

TOPICAL CORTICOSTEROIDS

The availability of nearly 400 topical preparations containing corticosteroids, alone or in combination with other drugs, attests to the popularity of such agents in the treatment of skin ailments. Some of this popularity is deserved, since topical steroids have a palliative effect in a number of common dermatoses, especially when used at the subacute stage. Except for fludrocortisone, none have any

systemic side effects even with prolonged use. They also lack allergenic sensitizing capacity, and they have almost unlimited stability in most vehicles. Their freedom from offensive odor, staining and irritation adds to their cosmetic acceptability.

INDICATIONS - Like other useful medicines, however, topical steroids are employed in many conditions in which they are ineffective, or in which their effectiveness is limited to the soothing action of the vehicle. Although authorities differ in listing the dermatoses in which these products are useful, the following are conditions in which they are generally considered to be helpful or at least worth a trial: localized neurodermatitis, such as anogenital pruritus; atopic dermatitis; nummular eczema; intertrigo; and some instances of eczematous contact dermatitis and seborrheic dermatitis.

Since topical steroids are expensive, only small amounts should be prescribed at first. If such medication is going to be helpful, it will generally show its effectiveness in 3 or 4 days. Some skin disorders not responsive to topical steroids, for example keloids and alopecia areata, are helped by local steroid injections. Judicious oral therapy is sometimes valuable in generalized or severe dermatoses; in fact, oral therapy has prolonged life and made comfortable existence possible for many patients with such disorders as pemphigus and systemic lupus erythematosus (see The Medical Letter, Jan. 23, 1959 for cautions on oral steroids). But the list of dermatoses in which topical steroids are helpful remains a limited one.

CHOICE OF PREPARATION - While opinions differ as to the relative effectiveness of the various topical steroids in skin ailments, it is doubtful that any of the newer preparations are clearly superior to hydrocortisone. (Cortisone, as was discovered early in the investigation of corticosteroids, has little if any effect when applied to the skin.) Some investigators consider triamcinolone acetonide to be more effective than other topical steroids, but there are no controlled studies to support this view. Prednisolone, triamcinolone acetonide, fluorometholone, hydrocortamate (or ethamicort), and fludrocortisone are all useful, and the new topical dexamethasone preparations seem to be equally active. Fludrocortisone, unlike the others, is absorbed through the skin in amounts sufficient to cause systemic side effects; therefore it should be used, if at all, with caution, especially near mucous membrane. With hydrocortisone, a 1% concentration (either as the acetate or free alcohol) is adequate in most cases. (One Medical Letter consultant reports good results with a 0.5% concentration.) Taking 1% hydrocortisone as the reference standard, the equivalent concentrations of the various topical steroids are:

Hydrocortisone 1%
Prednisolone 0.5% (Meti-Derm cream-Schering)
Fludrocortisone 0.1% (Alflorone ointment and lotion-Merck;
F-Cortef ointment-Upjohn; Florinef ointment and lotion-Squibb)
Hydrocortamate 0.5% (Magnacort ointment-Pfizer)
Triamcinolone acetonide 0.1% (Aristocort cream and ointment-Lederle;
Kenalog ointment, cream and lotion-Squibb)
Fluorometholone 0.025% (Oxylone cream-Upjohn)
Dexamethasone 0.1% (Decadron cream-Merck)

Considerably more important than the choice of corticosteroid is the choice of the vehicle in which it is dispensed. In general, acute and subacute eruptions tolerate lotions and water-miscible creams best, while chronic lesions respond better to greasy ointment bases. Aerosols are an expensive and probably ineffective way of administering topical steroids. The majority of patients are best treated with water-washable cream base preparations.

COMBINATION PREPARATIONS - The addition of other medications to the steroid is desirable only where there is a specific indication for both the steroid and the other medication. For example, the admixture with an antibiotic is beneficial only where a bacterial infection complicates a skin disorder amenable to steroid treatment. (Medical Letter consultants consider neomycin sulphate and terramycin the best antibacterial agents for such use, with either polymixin B or bacitracin the second choice.) The possibility of allergic dermatitis must be kept in mind, however, with the addition of other drugs (including neomycin) to the steroid, and the reaction may be partially masked by the steroid. Steroid preparations containing antihistamines or local anesthetics should be avoided; antihistamines used topically are ineffective, and both antihistamines and anesthetics frequently cause sensitization reactions.

CONTRAINDICATIONS - Except for fludrocortisone, little or no significant systemic absorption of topical corticosteroids has been noted, even after extensive and prolonged use. A number of observations testify to the marked percutaneous absorption of fludrocortisone, which may be sufficient to cause significant water retention and serum electrolyte imbalance. If this drug is used at all, it should be applied sparingly and only over very small surface areas. The few medical contraindications to any topical steroid therapy are thermal burns, herpes simplex, and varicella. (A 5-Gm. tube of 1% hydrocortisone ointment or the equivalent costs about $1.50 to $2; a 20-Gm. tube, about $3.50 to $4.50.)

QUADRIGEN AND TETRAVAX

Should polio vaccine be administered by itself to infants and to children under five years of age, or should it be given in combined form along with diphtheria, pertussis and tetanus antigens? Because this question is being raised by many physicians, The Medical Letter sought the opinions of a number of authorities. There was general agreement with the position of the American Public Health Association's Committee on Multiple Antigens favoring the use of the multiple preparations (Quadrigen--Parke-Davis; Tetravax-Merck). At the present time there appears to be no cause for concern about the potency of the polio vaccine in the combinations. Some pediatricians have reported what they regarded as an excessive incidence of reactions from the multiple product. But the New York City Board of Health and other pediatricians believe that the combination does not increase the over-all incidence of reactions. It should not be overlooked that young children are more likely to get the full course of polio injections with the use of the combination antigens. While it is true that children under 6 months get little benefit from polio vaccine because of the presence of antibodies from the mother, the subsequent booster doses, particularly the fourth, will give the full protection of the vaccine.

THE MEDICAL LETTER ON DRUGS AND THERAPEUTICS is published fortnightly by Drug and Therapeutic Information, a non-profit corporation, 136 E. 57th St., New York 22, N. Y. Second-class postage paid at New York, N. Y. The subscription fee is $12.50 per year ($6.25 for residents, internes and students).